Hepatic Encephalopathy Associated With Cancer or Anticancer Therapy

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ABSTRACT

Hepatic encephalopathy is an uncommon cause of neurologic deterioration associated with hyperammonemia, which results from hepatic dysfunction or altered ammonia metabolism. Often overlooked, hyperammonemia may occur via any of several pathophysiological processes, and in the setting of malignancy, it is a potentially reversible cause of confusion and coma. Hepatic dysfunction as a result of malignant infiltration, chemotherapeutic toxicities, targeted anticancer therapies, reactivation hepatitis, portosystemic shunting, and transarterial chemoembolization (TACE) is discussed, and an approach to etiological diagnosis and management is outlined.

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Hepatic encephalopathy (HE) occurs in the setting of hepatic dysfunction or altered ammonia metabolism and is characterized by neurologic disturbance ranging from subclinical impairment to coma and death. Hyperammonemia has been suggested as the common pathway through which neurologic damage is mediated and may develop as a result of a primary inborn error of metabolism or a secondary cause (Table 1). Malignancy and its treatment with conventional chemotherapy or targeted therapies have been implicated in the development of hyperammonemia through a multitude of mechanisms including malignant infiltration of hepatic tissue, chemotherapeutic or targeted-therapy toxicities, reactivation of viral hepatitis, portosystemic shunting, and transarterial chemoembolization (TACE). A discussion of each of these causes of hepatic encephalopathy follows.

Table 1. Causes of hyperammonemia

Primary (*congenital*)
1. Inborn errors of metabolism
Secondary (*acquired*)
1. Liver disease
2. Gastrointestinal bleeding
3. Renal disease
4. Urinary tract infections
5. Ureterosigmoidostomy
6. Parenteral nutrition
7. Reye's Syndrome
8. Chemotherapy
9. Drugs
10. Bone marrow transplantation
11. Solid organ transplantation
12. Severe muscle exertion
13. Septic shock

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PATHOPHYSIOLOGY

Ammonia, a nitrogenous waste product of amino acid catabolism, is produced primarily by colonic flora breakdown of amino acids and urea, by enterocyte metabolism of glutamine, and by glutamine metabolism within the kidneys.[1] Ammonia produced from the gut is transported to the liver via the portal circulation where, in the intact liver, it is converted to the nontoxic water-soluble metabolite urea, which is subsequently excreted by the kidneys. This process, known as the urea cycle, is dependent on the normal functioning of six enzymes; *N*-acetylglutamate synthetase, carbamyl phosphatase synthetase, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, and arginase, which are present within periportal hepatocytes. In the normal liver, approximately 90% of portal ammonia is metabolized to urea in this fashion.

The primary site of ammonia toxicity appears to the central nervous system.[2,3] In the brain, excess ammonia is converted to glutamine within astrocytes via glutamine synthetase. The accumulation of osmotically active glutamine causes intra-astrocytic edema and Alzheimer's type II change, primarily within the frontal and occipital white matter, the globus pallidus, the putamen, and the anterior limb of the internal capsule.[4,5] This phenomenon is further complicated by the development of oxidative stress, the process of which is not clearly understood but is most likely a consequence of astrocyte swelling and glutamine-mediated production of mito-

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chondrial reactive oxygen species.[6,7] The combined effects of astrocytic edema and oxidative stress are suggested to alter overall astrocytic functioning and gene expression, with interference of normal glioneuronal communication, disruption of synaptic plasticity, and subsequent development of encephalopathy.[5] Cytokine release, particularly tumor necrosis factor-α, and hyponatremia have also been shown to promote astrocytic swelling and may compound the effects of hyperammonemia.[8] This finding may account for the observation that some patients develop hepatic encephalopathy despite stable or minimal increases in ammonia, but in the setting of superimposed infection or electrolyte disturbance.

MALIGNANT INFILTRATION

Although liver infiltration is common among metastatic malignancies, the development of hepatic failure and encephalopathy is a rare occurrence. A review of the documented case reports suggests that hematologic malignancies are the most commonly implicated, predominantly non-Hodgkin's lymphoma (NHL). Cases of solid tumors (excluding hepatocellular carcinoma) causing encephalopathy have also been reported, most often from primary sites with hepatic drainage, including gastric, pancreatic, and colon cancer, as have cases of melanoma and small cell lung cancer.[9–13] The pathophysiology of hepatic encephalopathy associated with tumor infiltration is not well understood; however, where acute liver failure is present, histologic studies suggest obstruction of hepatic venules or sinusoidal infiltration with subsequent hepatic ischemia and necrosis or overwhelming replacement of hepatic tissue as the most likely causes.[14–17] A case series of patients with encephalopathy and acute liver failure revealed diffuse infiltrating cells and large areas of necrosis present in all histologic samples, regardless of the underlying malignancy.[10] Of note, in that series there was no evidence of localized or focal cell aggregations, as is commonly seen with liver metastases.

In contrast to other hematologic and solid tumors, hepatic encephalopathy occurs frequently with primary hepatocellular carcinoma (HCC). A recent retrospective analysis of 276 patients with HCC concluded that encephalopathy was present in approximately 18% of patients at the time of diagnosis.[18] In this analysis, encephalopathy present at diagnosis occurred exclusively in patients with hepatitis C virus (HCV)–related HCC and was not seen at diagnosis with hepatitis B virus (HBV)–related HCC. Regardless of etiology, the incidence of encephalopathy increases with the severity of disease and is also associated with treatment including biologic therapy and chemoembolization, discussed in further detail later. At the end stages of HCC, intractable encephalopathy almost invariably occurs in most patients.

Neuroendocrine tumors (NETs) also appear to have a particular predilection for hyperammonemic encephalopathy (HE). In reported cases, HE often occurs in the absence of hepatic failure and without any evidence of acquired urea cycle dysfunction.[19–22] It has been suggested that portosystemic shunting is the underlying etiology, although it is not observed in all cases. Alternatively, as yet unknown hormone or neurotransmitters produced by NETs may predispose to the development of HE.[20]

CHEMOTHERAPY-RELATED HEPATIC ENCEPHALOPATHY

The etiology of HE during chemotherapy is still poorly understood. The large number of potential causative agents, use of combination chemotherapy, and paucity of events make elucidating the pathophysiological processes difficult. Case reports of a multitude of agents have been documented, including 5-fluorouracil (5-FU), L-asparaginase, cytarabine, cyclophosphamide, vincristine, etoposide, daunorubicin, busulfan, methotrexate, amsacrine, topotecan, vinorelbine, and gemcitabine, as well as biologic therapies, including sorafenib, imatinib, and possibly rituximab.[23–31]

5-FU, a fluoropyrimidine analog commonly used in combination chemotherapy regimens for colon, breast, and gastric cancers, has been observed to cause an idiosyncratic form of HE that occurs in the absence of hepatic impairment. A retrospective analysis showed 5.7% of patients receiving high-dose 5-FU (HDFL) treatment developed encephalopathy associated with marked hyperammonemia and lactic acidosis in the absence of hepatic failure or any other metabolic or structural abnormality.[32] The cause of HE during 5-FU therapy is unclear, but may be related to accumulation of ammonia, the end product of 5-FU breakdown, in combination with impairment of the ATP-dependent urea cycle by fluoroacetate, an intermediate breakdown product of 5-FU.[32,33] The onset of HE occurs in the first 0 to 4 days after chemotherapy, and most cases resolve spontaneously within 1 to 2 days after discontinuation of 5-FU.[30,33,34]

Agents used in the treatment of acute myeloid leukemia have also been associated with HE.

L-Asparaginase, which acts by depriving leukemic cells of asparagine, has been associated with a form of HE, presumably related to an acquired urea cycle defect.[24] It deaminates asparagine and metabolizes glutamine, both of which lead to accumulation of ammonia. In an analysis of two patients who developed HE after L-asparaginase administration, elevated ammonia, glutamic acid, and phenylalanine were observed. A follow-up observation of other patients treated with L-asparaginase revealed hyperammonemia in all cases, but encephalopathy developed only in those who also had concomitant elevated phenylalanine, which was thought to be related to ondansetron administration.[35] Cytosine arabinoside (cytarabine or Ara-C) was suggested to precipitate HE via increased ammonia generation as a result of cytarabine deamination; however, a recent case report suggested that deamination may contribute less than 5% of total body ammonia generation, a finding that casts doubt on this conclusion.[34] Fulminant hepatitis may also present as encephalopathy, and the agents melphalan, azathioprine and its metabolite 6-mercaptopurine, dacarbazine, and temozolamide are occasional causes.[36–39] The etiology of HE observed with other agents used in combination induction regimens including cyclophosphamide, vincristine, etoposide, daunorubicin, and amsacrine remains unclear.

HE RELATED TO TARGETED ANTICANCER THERAPIES

Sorafenib and sunitinib, two new multitargeted tyrosine kinase inhibitors, have also been associated with the development of an idiopathic hepatic encephalopathy. Lee et al[40] reported two cases of HE developing 17 and 10 days after initiation of sunitinib

for gastrointestinal stromal tumor (GIST), both of which resolved within 24 hours of sunitinib withdrawal and treatment with lactulose. In one patient, sunitinib was restarted at a lower dose, and HE redeveloped 7 days after reintroduction. In addition, Marks et al[41] reported the development of confusion and asterixis occurring 20 days after sorafenib initiation for HCC, which resolved within 24 hours of withdrawal of the drug, recurred 8 days after drug reintroduction at a lower dose, and again resolved within 24 hours of withdrawal; in this case, ammonia level was not reported. These cases exhibited a remarkable similarity in presentation, and although the underlying mechanism is unclear, it appears to be related to a class effect. Imatinib, a tyrosine kinase inhibitor used in the treatment of Philadelphia chromosome–positive leukemia and gastrointestinal stromal tumors, and ipilimumab, an anti-CTLA-4 antibody used in the treatment of metastatic melanoma, are also associated with a fulminant hepatitis that may be fatal.[42–44]

REACTIVATION OF VIRAL HEPATITIS

First reported in 1975, the administration of chemotherapy to patients with pre-existing chronic viral hepatitis can result in HE and fatal hepatic failure.[45] Hepatocyte dysfunction and destruction occur as a result of direct viral and immunologic toxicity, and subsequent reduced ammonia metabolism may result in HE. Reactivation hepatitis, associated with chronic hepatitis B (HBV) reactivation, is implicated more commonly than is hepatitis C (HCV) and occurs in three stages. The first stage is characterized by immunosuppression due to chemotherapy and subsequent uncontrolled viral replication. Serum viral markers including HBV DNA, hepatitis B surface antigen (HBsAg), and HCV RNA are increased, and some direct viral cytotoxicity may occur. This stage persists for at least as long as immunosuppression remains, and a return of immune surveillance heralds the onset of the second stage. As immunity returns, infected hepatocytes are destroyed, and jaundice and clinical hepatitis may develop. The third stage, or recovery phase, involves clearing of virus, resolution of hepatitis, and re-establishment of viral control.[46,47] All three stages may not occur in every patient. For example, in a patient in whom immunosuppression does not abate, the second stage may not occur, and elevated viral replication may persist. Allogeneic stem cell transplants and solid organ transplantation are well-documented situations in which this may occur.[48,49] A third stage may be partial, with residual chronic hepatitis, or will not occur in patients in whom the second stage is so severe as to be fatal.

Hepatitis B

Patients with chronic HBV infection are those predominantly at risk of reactivation (). Because prophylactic treatment is available and successful, screening has become a topic of debate. In practice, a recent statement by the American Society of Clinical Oncology (ASCO) highlighted the paucity of prospective data and suggests screening with HBsAg, possibly in conjunction with antihepatitis B core antigen (anti-HBc) in high-risk populations.[50] Patients with HbsAg have chronic infection and are at most risk; patients with isolated anti-HBc positivity may have occult infection and should be investigated further, as reactivation is also possible in this subgroup.[51] A multivariate analysis performed by Yeo et al[52] suggested that malignancies associated with highest risk are lymphoma and breast cancer that increase the risk 5 times and 4.2 times, respectively. A detectable HBV viral load has also been shown to confer a risk in excess of 8 times greater than that of an undetectable viral load.[52,53] Male sex, HBeAg positivity, and treatment with steroid, anthracycline, or rituximab are also associated with an increased risk.[54,55] (See Table 2 for risk factors discussed in References 52–55.) Prophylactic antiviral therapy for patients who are HBsAg and/or HBV DNA positive is now widely accepted and has been validated in two prospective trials.[56,57] The choice of antiviral agents is complex and will not be discussed here.

Table 2. Risk Factors for HBV Reactivation

Detectable HBV viral load
Lymphoma or breast cancer
Male sex
HBeAg positivity
Steroid, anthracycline, or rituximab use

Hepatitis C

Reactivation of HCV occurs less frequently than HBV. Reactivation has not been documented in patients who have cleared the infection (shown by an undetectable HCV viral load), and thus only patients with a detectable viral load are at risk of reactivation.[58] Case series and reports suggest it occurs more commonly in hematologic malignancies, but it has also been documented in solid tumors.[59–61] Risk factors for HCV reactivation are poorly understood. There is some evidence that genotype 2a confers an additional risk, but this has yet to be confirmed.[62] Corticosteroids appear to be the most common agent associated with reactivation, although recently, treatment with rituximab has also variably been reported as a risk factor.[63–65]

Clinical hepatitis usually develops weeks to months after treatment and is heralded by elevated aminotransferases and a rise in HCV viral load. The severity of hepatitis is variable but may be as severe as fulminant hepatic failure and death.[66] Appropriate treatment has not yet been determined, and at present, cessation of chemotherapy and supportive treatment are the mainstays of care.

PORTOSYSTEMIC SHUNTING

Portosystemic shunting occurs when venous blood from the gut bypasses the hepatic sinusoids and re-enters the systemic venous blood without exposure to hepatic metabolism. In patients with malignancy, it may be encountered in the setting of portal vein thrombus, Budd-Chiari syndrome, or transtumoral portosystemic shunt. Although malignancy accounts for 21% to 24% of portal vein thrombosis, it is a relatively infrequent finding in clinical practice. The clinical presentation rarely includes encephalopathy, and hepatic and pancreatic tumors are most commonly implicated.[19,67] In contrast, HE is present in 9% of patients with Budd-Chiari syndrome, which has been documented in virtually every type of malignancy.[68] Primary Budd-Chiari syndrome, or hepatic vein obstruction by thrombus, is more commonly associated with myeloproliferative neoplasms, whereas secondary Budd-Chiari syndrome,

obstruction of the hepatic vein by tumor, occurs more commonly as a result of HCC or other solid tumor.[69] Transtumoral shunting is an exceedingly rare cause of HE, but has been reported in a patient with a hepatic metastasis of a pancreatic islet cell carcinoma and may be implicated in some cases of HE occurring in metastatic NETs.[19,70]

TACE-RELATED HE

TACE is an emerging treatment modality primarily used in the treatment of HCC and in some cases of hepatic metastases. The therapy was initially associated with a mortality of up to 10%, but modern techniques are now associated with major complication rates of approximately 0.5%, of which hepatic failure, including HE, accounts for 40%.[71,72] HE following TACE occurs primarily as a result of hepatic failure and poor functional hepatic reserve, high-dose chemoembolization, and multiple procedures are associated with an increased risk.[73]

DIAGNOSIS

HE should be should be suspected in all cases of neurologic decline with malignancy. Initial investigations should include a basic blood evaluation and measurement of ammonia (Table 3). Once confirmed, more specific testing can be undertaken to determine the etiology. Elevated ammonia, usually greater than 200 μmol/L in the absence of significant liver dysfunction, should prompt a consideration of idiopathic HE associated with chemotherapeutics such as 5-FU or L-asparaginase or the presence of portosystemic shunting. Quantitative plasma amino acids and urine orotic acid may be useful in diagnosing inborn or acquired urea cycle defects. Particular patterns of note are raised glutamic acid and phenylalanine associated with L-asparaginase therapy or elevated urinary orotic acid, a marker of ornithine transcarbamylase (OTC) deficiency, one of the few inborn errors of metabolism that may present in adulthood. Normal or mildly elevated amino acids are common in the setting of chemotherapy and are unlikely to be significant.

Abdominal ultrasound with Doppler studies has historically been the initial imaging modality of choice for the evaluation of splanchnic vein thrombosis and has a reported sensitivity and specificity of approximately 90%.[74] Contrast-enhanced abdominal CT has equivalent diagnostic accuracy and offers more information regarding collateral circulation, and in the setting of malignancy, the additional information offered regarding disease status makes it the imaging modality of choice.[75] CT of the brain is also indicated to exclude other causes of neurologic deterioration, including brain metastases, infection, or leptomeningeal disease.

HE in the setting of significant hepatitis and hepatic synthetic failure may be due to a hepatotoxic effect of chemotherapy, reactivation hepatitis, or malignant infiltration of the liver. In such a case, investigations should include viral hepatitis serology or viral load in the setting of known hepatitis B or C and a consideration of a liver biopsy. A rise in HBV DNA or HCV RNA of more than 1 $\log_{10}$ IU/mL with concurrent liver enzyme derangement is characteristic of reactivation in patients with known viral hepatitis.[46,47] In cases in which the etiology of hepatitis is unclear, a liver biopsy may be critical in determining the difference between progressive disease and chemotherapeutic toxicity, as malignant infiltration is not always evident on imaging studies.[10]

Table 3. Investigations for suspected HE

Blood evaluation
Ammonia level
Complete blood count with differential
Electrolytes, BUN, creatinine
Liver function tests: AST, ALT, GGT, ALP, bilirubin, albumin
Coagulation studies: APTT, PT/INR
LDH and lactate
Glucose
Arterial blood gas
Imaging studies
Brain CT
Abdominal US or CT
Additional testing for idiopathic HE
Plasma amino acids
Urine orotic acid
Additional testing for HE associated with hepatic failure
Hepatitis serology
Quantitative HBV or HCV viral load (where appropriate)
Liver biopsy

BUN, blood urea nitrate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; LDH, lactate dehydrogenase; CT, computed tomography; US, ultrasound; HBV, hepatitis B virus; HCV, hepatitis C virus.

MANAGEMENT

The management of hepatic encephalopathy is centered on reducing plasma ammonia, primarily by reducing gut production and absorption, but may also be achieved via enhanced renal excretion. Lactulose, a nonabsorbable disaccharide, has long been the mainstay of treatment; however, the mechanism of action in reducing encephalopathy is poorly understood. It is suggested that lactulose acts by lowering colonic pH with subsequent ammonium trapping, promoting a shift in colonic flora to non–urase-producing bacteria and mass removal of colonic bacteria through catharsis.[76] The nonabsorbable antibiotic rifaximin has also been shown to be at least as effective as lactulose in the treatment of acute encephalopathy.[77] Dietary measures, such as protein restriction, have not been shown to be of use and in fact may precipitate starvation physiology, which may be detrimental to outcomes.[78,79]

Sodium benzoate and sodium phenylacetate convert glycine to hippurate and glutamine to phenylacetate glutamine (PAG), respectively. Hippurate and PAG are nonurea forms of ammonia freely excreted by the kidneys. They have been shown to be effective in the management of encephalopathy due to urea cycle defects in robust trials although they are not commonly used in other forms of hepatic encephalopathy.[80] There are case reports of successful treatment of chemotherapy-induced HE with these agents, although no clinical trials in this situation have been identified.[81]

Hemodialysis is usually used in cases refractory to medical management. It is effective in clearing ammonia, either via intermittent hemodialysis or continuous arteriovenous or venovenous hemofiltration. Plasma ammonia levels usually fall sharply, and dialysis may be ceased after levels fall below 200 μmol/L.[82] Alternative manage-

ment should be administered concurrently, as rebound may occur after cessation of dialysis. Careful consideration of goals of care should be undertaken before initiation of dialysis, as outcomes are often poor, and underlying progression of malignancy must be ruled out before commencement. Patients offered dialysis are usually markedly unwell and have failed alternative management; hence, fatal outcomes are commonly reported and in survivors, long-term prognosis is often poor.[19,31,34]

TACE has been attempted in two documented cases of idiopathic HE in the setting of metastatic NETs and was successful in one report.[20,21] Hepatic impairment has usually been regarded as a contraindication to TACE; however, it has been widely and safely employed as palliative management for metastatic NETs, and in carefully selected patients with isolated hyperammonemia, it could be considered.

CONCLUSIONS

HE in the setting of malignancy may occur as a result of several pathologic processes. In general, encephalopathy is either associated with hepatic failure or develops as a result of an idiopathic hyperammonemic process. Malignant infiltration, hepatotoxic drug reactions, reactivation of viral hepatitis, and TACE may present as encephalopathy in the setting of hepatic failure, and viral hepatitis serology, evaluation of concurrent drugs, and consideration of a liver biopsy should be undertaken. In contrast, hyperammonemia in the absence of hepatic failure may be due to idiosyncratic drug reactions, particularly 5-FU and L-asparaginase; inborn errors of metabolism, particularly OTC deficiency; or portosystemic shunting. Plasma and urinary amino acids and imaging studies are of most importance in these cases. Management has remained largely unchanged, and lactulose or rifaximin remain the mainstays of supportive care. Sodium benzoate and sodium phenylacetate may be used in patients with suspected acquired or inborn urea cycle defects, and dialysis can be considered as a last-line therapy but should be reserved for patients in whom an obvious reversible precipitant is identifiable, as outcomes are poor.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.